

**Remarks**

Claims 1-10 and 12-42 are pending in the present application. Claim 11 has been cancelled without prejudice. The following rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claims 1-42 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
2. Claims 1-5, 10, 18, 20-21, and 41 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Inaba (J. Surg. Res. 78:31-36 (1998));
3. Claims 1, 18, 20-21, 27-31, and 40-42 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Primus (Cancer Res. 53:3355-61 (1993));
4. Claims 1, 18, 20-21, 27-31, and 40-42 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Dranoff (U.S. Pat. No. 5,637,483);
5. Claim 41 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-76 (1996));
6. Claims 1-11, 18-21, 27-34, and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor in view of Inaba;
7. Claims 1-21, 27-34 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba in view of Clontech (CLONTECHniques, 4/1999 and further in view of Hoatlin (J. Mol. Med. 73:113-20 (1995));
8. Claims 1-14, 16-21, 25, 27-34, and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Naldini (Science 272:263-67 (1996));
9. Claims 1-11, 18-24, 27-34, 39 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Primus and Deng (Biotechniques 25:274-279 (1998));
10. Claims 1-11, 18-21, 26-38 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Schroder; and
11. Claims 1-11, 18-21, 26-38 and 41-42 stand rejected under 35 U.S.C. §103 as

allegedly being obvious over Mathor and Inaba, and further in view of Dranoff.

Claims 1, 12, 13, 21, 29, 32-34, 39, 41, and 42 have been amended and Claims 11 and 19 have been canceled in order to further Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000)), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. None of the claim amendments made herein are intended to narrow the scope of any of the amended claims within the meaning of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

**1. The Claims are Definite**

Claims 1-42 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The claims have been amended per the Examiner's suggestions. In particular, claim 1 has been amended to delete the reference to an "integrating" vector, claims 12 and 13 no longer refer to steps a and b, claim 19 has been cancelled, claim 21 now recites a "segment encoding a secretion signal sequence," claim 20 now refers to a "retroviral vector" and a "segment encoding a secretion signal sequence," claims 32-34 now refer to "clonally selected" host cells, and claim 42 now refers to "retroviral vectors" and steps a and b. Accordingly, each of the Examiner's grounds for rejection have been addressed and Applicants respectfully request removal of these rejections.

**2, 3, 4, 5. The Claims are Novel Over the Cited References**

Claims 1-5, 10, 18, 20-21, and 41 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Inaba (J. Surg. Res. 78:31-36 (1998)); Claims 1, 18, 20-21, 27-31, and 40-42 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Primus (Cancer Res. 53:3355-61 (1993)); Claims 1, 18, 20-21, 27-31, and 40-42 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Dranoff (U.S. Pat. No. 5,637,483); and Claim 41 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-76 (1996)).

The Federal Circuit has stated the relevant analysis for anticipation as follows:

A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference.

*Verdegaal Bros. v. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Independent claims 1 and 42 now require transduction at a multiplicity of infection (MOI) from about 10 to 1000 and for the process to result in from 10 to 100 retroviral integrations in a host cell. None of the cited references teach repeated transductions at high MOIs and the production of host cells with from 10 to 100 integrated retroviral vectors. Claim 41 has been amended to require more than 20 integrated retroviral vectors. As such, the claims are not anticipated by the cited references. Applicants respectfully request that these grounds of rejection be removed.

**6. The Claims are Not Obvious Over Mathor and Inaba**

Claims 1-11, 18-21, 27-34, and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor in view of Inaba. A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and without more entitles the Applicants to allowance of the claims in issue. See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). Applicants respectfully submit that the cited references neither teach nor suggest each element of the claims, that a proper basis for combining the references has not been established, and that there is no reasonable expectation of success for achieving the claimed process.

First, the cited references in combination do not teach each element of the claims. As amended, the claims require repeated transductions at a high (10-1000) MOI. The Examiner alleges that Mathor teaches the use of an MOI of at least 100. However, Applicants respectfully submits that Mathor teaches no such thing. In particular, the Examiner alleges the Materials and Methods of Mathor teach that the titer of vector used by Mathor was  $10^6$  cfu/ml and that the keratinocytes were seeded at  $5 \times 10^3$  cells/cm<sup>2</sup>. However, careful examination of the Materials

and Methods section reveals that the volume of vector solution used to transduce the cells is not known and moreover that the stage of culture at which the cells were transduced is not known. Thus, neither the number of vectors nor the number of cells to which the vectors were applied is known. Absent this information, there is no way to know what the MOI was, although Applicants suggest that it was probably less than 1 based on the low titer of the vector that was used. In contrast, the Applicants process typically uses titers of  $10^7$  to  $10^9$  to achieve high MOI levels. Thus, neither reference cited by the Examiner teaches the claimed MOI. As such, a prima facie case of obviousness has not been established and applicants respectfully request that this ground of rejection be removed.

Second, there is no motivation to combine the references. Even if Mathor did teach transduction at a high MOI (and Applicants contend that it does not), there is no motivation to perform serial transductions at high MOI. In the Office Action for related application 10/397,079, the Examiner admitted that one of skill in the art would not be motivated to use the sequential process to produce the claimed number of integrations for fear of insertional mutagenesis. In support of this argument, the Examiner cited to both Coffin: "Insertional mutagenesis by retroviral vectors is often cited as a safety concern . . . . In situations where relatively few cells are modified, as in the case of gene transfer into rare hematopoietic stem cells, the total number of insertion sites will also be small, and the risks are expected to be very low. The risks are higher in cases where large numbers of cells are transduced, which increases the number of independent integration events. . . ." and Arai (Virology 260:109-115 (1999)): "high levels of proviral integration could result in 'insertional mutations in essential genes.'"

Applicants respectfully remind the Examiner that where references teach away from the claimed invention, there can be no motivation to combine. *See Tec Air, Inc. v. Denso Manufacturing Michigan, Inc.*, 192 F.3d 1353 (Fed. Cir. 1999). In this instance, there is no motivation to combine the references because even if a use of a MOI was taught, a person of skill in the art would not use a high MOI in serial transduction process for fear insertional mutagenesis.

Third, there is no reasonable expectation of success in arriving at the claimed invention. Applicants again point to the Examiner's reasoning in related application 10/397,079: "As retroviral insertion appears to be an essentially random event, the nature of retroviral insertion events is highly unpredictable." Thus, based on the Examiner's own reasoning, the prior art

provides no reasonable expectation of success in achieving the claimed integration levels using the claimed process because of the unpredictable nature of retroviral integrations.

In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**7. The Claims are not Obvious Over Mathor, Inaba, Clontech and Hoatlin**

Claims 1-21, 27-34 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba in view of Clontech (CLONTECHniques, 4/1999 and further in view of Hoatlin (J. Mol. Med. 73:113-20 (1995)). For the sake of brevity, the same arguments apply to this rejection as to the rejection over Mathor and Inaba. Clontech and Hoatlin do not cure the deficiencies noted above. In particular, the combined references do not teach repeated transductions at a high MOI, as required by the claims. Moreover, even if transduction at a high MOI was taught, there is no motivation to combine the references due to the fact that the art teaches away from the desirability of high levels of proviral integrations. Likewise, the references do not provide a reasonable expectation of success for achieving the claimed inventions because of the admitted unpredictability of retroviral insertions. In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**8. The Claims are not Obvious Over Mathor, Coffin and Naldini**

Claims 1-14, 16-21, 25, 27-34, and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Naldini (Science 272:263-67 (1996)). For the sake of brevity, the same arguments apply to this rejection as to the rejection over Mathor and Inaba. Inaba does not cure the deficiencies noted above. In particular, the combined references do not teach repeated transductions at a high MOI, as required by the claims. Moreover, even if transduction at a high MOI was taught, there is no motivation to

combine the references due to the fact that the art teaches away from the desirability of high levels of proviral integrations. Likewise, the references do not provide a reasonable expectation of success for achieving the claimed inventions because of the admitted unpredictability of retroviral insertions. In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**9. The Claims are not Obvious Over Mathor, Inaba, Primus and Deng**

Claims 1-11, 18-24, 27-34, 39 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Primus and Deng (Biotechniques 25:274-279 (1998)). For the sake of brevity, the same arguments apply to this rejection as to the rejection over Mathor and Inaba. Primus and Deng do not cure the deficiencies noted above. In particular, the combined references do not teach repeated transductions at a high MOI, as required by the claims. Moreover, even if transduction at a high MOI was taught, there is no motivation to combine the references due to the fact that the art teaches away from the desirability of high levels of proviral integrations. Likewise, the references do not provide a reasonable expectation of success for achieving the claimed inventions because of the admitted unpredictability of retroviral insertions. In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**10. The Claims are not Obvious Over Mathor, Inaba and Schroeder**

Claims 1-11, 18-21, 26-38 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Schroeder. For the sake of brevity, the same arguments apply to this rejection as to the rejection over Mathor and Inaba. Schroeder does not cure the deficiencies noted above. In particular, the combined references do not teach repeated transductions at a high MOI, as required by the claims. Moreover, even if transduction at

a high MOI was taught, there is no motivation to combine the references due to the fact that the art teaches away from the desirability of high levels of proviral integrations. Likewise, the references do not provide a reasonable expectation of success for achieving the claimed inventions because of the admitted unpredictability of retroviral insertions. In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**11. The Claims are not Obvious Over Mathor, Inaba and Dranoff**

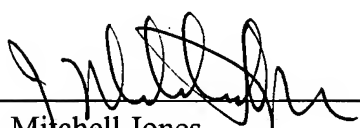
Claims 1-11, 18-21, 26-38 and 41-42 stand rejected under 35 U.S.C. §103 as allegedly being obvious over Mathor and Inaba, and further in view of Dranoff. For the sake of brevity, the same arguments apply to this rejection as to the rejection over Mathor and Inaba. Dranoff does not cure the deficiencies noted above. In particular, the combined references do not teach repeated transductions at a high MOI, as required by the claims. Moreover, even if transduction at a high MOI was taught, there is no motivation to combine the references due to the fact that the art teaches away from the desirability of high levels of proviral integrations. Likewise, the references do not provide a reasonable expectation of success for achieving the claimed inventions because of the admitted unpredictability of retroviral insertions. In summary, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness because the cited references do not teach each element of the claims, the references are not properly combined, and the references do not establish a reasonable expectation of success. Accordingly, Applicants request that this ground of rejection be removed.

**C O N C L U S I O N**

All grounds of rejection and objection of the Office Action of May 18, 2005 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the

undersigned collect at (608) 218-6900.

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